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(54)【発明の名称】 ポリスルホン系血液処理膜

(57)【要約】

【課題】 膜中の可溶性環状二量体の含有率が低く、不溶性凝集物を事实上含まないことにより、抗血栓性に優れるポリスルホン系血液処理膜を提供する。

【解決手段】 ポリスルホン系高分子とポリビニルビロリドンからなる多孔質膜において、ポリスルホン系高分子に対する可溶性環状二量体の含有率を一定値以下に低減させた膜は、膜表面に不溶性凝集物が事实上存在しない。よって、血液を流した際に、該凝集物に起因する血小板の活性化が起こらず、抗血栓性に優れるため、血液浄化分野で好適に使用できる。

### 【特許請求の範囲】

【請求項1】 ポリスルホン系高分子とポリビニルビロリドンからなる多孔質膜において、該膜中のポリスルホン系高分子に対する可溶性環状二量体の含有率が1.0重量%以下であることを特徴とするポリスルホン系血液処理膜。

【請求項2】 血液接触面におけるポリビニルビロリドン濃度が25~50重量%であることを特徴とする請求項1に記載のポリスルホン系血液処理膜。

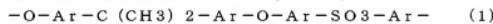
### 【発明の詳細な説明】

#### 【0001】

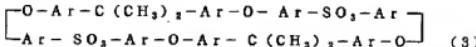
【発明の属する技術分野】 本発明は、体外循環による血中老廃物の除去を目的とする膜に関するもので、血液浄化、とりわけ血液透析、血液濾過、および血液濾過透析等の分野で利用されるものである。

#### 【0002】

【従来の技術】 近年、膜分離技術が数多く実用化されており、液体や気体の混合物から目的物を分離したり、不純物を除去するために様々な選択性分離膜が利用されている。選択性分離膜の素材としては、一般に有機系高分子が汎用されており、例えば、天然高分子としてセルロース、合成高分子としてはポリアクリロニトリル、ポリアミド、ポリイミド、ポリオレフィン、ポリシロキサン、ポリスルホン、ポリメタクリレート等が挙げられる。中でもポリスルホン系高分子は、工業用分離膜として幅広く利用されているが、その理由は、放射線、加熱、および酸・アルカリ等の化学薬品に対して優れた耐性を示すためである。また、生体適合性や安全性にも優れることから、最近では医療用分離膜の素材としても注目され、需要が増加している。ところが、ポリスルホン系高分子には重合にともなう副生成物の一つとして、ポリスルホンの可溶性環状二量体が含まれており、製膜原液の調整直後は溶解しているものの、以後経時的に結晶化して不溶性凝聚物となる。これがそのまま取り込まれて膜表面に析出すると、血液との接觸時に血小板を活性化し、結



第二の成分はポリスルホン系高分子に含まれる可溶性環状二量体であり、重合原料であるビスフェノールAとジクロロジフェニルスルホンが交互に二分子ずつ縮合して環化したものである。化学構造式は下記(3)に示され



【0008】 ポリスルホン系高分子に対する可溶性環状二量体の含有率は、膜あるいは原料樹脂を溶媒に溶かし、高速液体クロマトグラフィーで定量分析して算出される。一般的な湿式筋法で製膜する場合、可溶性環状二量体は通常用いられる凝固浴や洗浄水にはまったく溶解せず、そのまま膜中に取り込まれているため、膜中の

果として抗血栓性を低下させるおそれがあった。

#### 【0003】

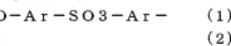
【発明が解決しようとする課題】 本発明は、膜表面に不溶性凝聚物を事实上含まないようにすることにより、抗血栓性に優れるポリスルホン系血液処理膜を提供することを目的とする。

#### 【0004】

【課題を解決するための手段】 本発明者らは、前記課題を解決するために観察検討した結果、1) ポリスルホン系高分子に含まれる可溶性環状二量体の一部が経時的に結晶化して不溶性凝聚物を形成すること、2) 膜表面に存在する不溶性凝聚物の量は、膜中の可溶性環状二量体の含有率に対応していることを見出した。その詳細な理由は明確ではないが、ポリスルホン系高分子に対する可溶性環状二量体の含有率が高い場合、ポリスルホン系高分子の分子鎖に溶解しきれない環状二量体が遊離し、溶媒中では不安定なために互いに凝聚して不溶化するものと推定される。したがって、膜中の可溶性環状二量体の含有率が一定値以下の場合、膜表面には不溶性凝聚物が事实上認められず、このような膜では抗血栓性が優れていることが分かった。

【0005】 すなわち、本発明は、ポリスルホン系高分子とポリビニルビロリドン(以下、PVPという)からなる多孔質の血液処理膜において、該膜中のポリスルホン系高分子に対する可溶性環状二量体の含有率が1.0重量%以下であることを特徴としている。本発明の膜を構成する第一の成分はポリスルホン系高分子である。下記の化学構造式(1)、もしくは(2)をユニットとした繰返し構造を有する芳香族ポリスルホン系高分子であり、芳香環に官能基やアルキル基が付加された、いわゆるポリスルホン誘導体や変成ポリスルホンであってもよい。なお、式中のArはパラ置換の二価フェニル基を示す。これらポリスルホン系高分子の分子量は特に限定しない。

#### 【0006】



る。

#### 【0007】

#### 【化1】

該含有率は1.4~2.0重量%となる。このような膜では、膜表面に不溶性凝聚物の析出が見られることがある。

【0009】 本発明の膜は、後述のようにPVPによつて膜表面が均一に親水化されているが、不溶性凝聚物はPVPを含まないため、膜表面に疎水性の強い部分が点

在することになる。また、膜表面に凝集物が点在すると局所で血流の微小な乱れが生じ、血小板にズリ応力がかかる可能性もある。これらの結果として、血小板の活性化が起こり、膜の抗血栓性が低下するものと考えられる。可溶性環状二量体の含有率が1.0重量%以下であれば、膜表面に不溶性凝集物は事実上観察されず、疎水性部分が点在しないので抗血栓性が低下するおそれはない。

【0010】可溶性環状二量体の含有率が低い膜を得る方法は、本発明の範囲には含まれず、公知の手段を利用すればよい。ただし、製膜後に洗浄するとPVPの一部も同時に洗浄除去され、膜表面の親水性が損なわれて血凝固を引き起すため、膜洗浄は避けるべきである。市販のポリスルホンを精製してから製膜する方法が好ましく、例えば、ポリスルホン系高分子を良溶媒に溶解した後、ポリスルホン系高分子に対しては貧溶媒で、しかも、可溶性環状二量体を溶解する溶媒中に再沈殿させて回収する方法がある。また、ポリスルホン系高分子を良溶媒に溶解した後、1~5%程度の水分を添加して強制的に不溶性凝集物を発生させ、漏過あるいは遠心分離で分別除去する方法、さらに、分取クロマトグラフィーにより可溶性環状二量体を含まない画分を分取する方法等も考えられる。いずれの方法を選択してもさしつかえはない。

【0011】本発明の膜を構成する第三の成分はPVPである。ポリスルホン系高分子自体は疎水性が強く、血液や透析液といった水性媒体には漏れにくい。また、疎水性が原因で血小板活性化して血液凝固が起こりやすい。そのため、血液処理膜としては、少なくとも血液と接触する膜表面が十分に親水化されている必要がある。製膜工程で膜を洗浄しても、ある程度疎表面に残存して親水性を発揮し、しかも、不必要な荷電を持たない中性の水性高分子としてPVPが好適である。

【0012】一方、物質透過性の点から膜表面のPVP濃度には最適な範囲が存在する。過剰に存在すると膨潤による膜の細孔半径の低下が著しく、物質透過性能が低下するが、少なすぎても漏過速度が確保できない。したがって、血液と接触する膜表面のPVP濃度は2.5~5.0重量%であることが好ましく、低分子蛋白の除去率を上げるために2.5~3.5重量%であることがさらに好ましい。膜の形態については特に限定せず、平膜でも中空糸膜でもさしつかえない。しかし、効率よい物質透過性を確保するには、物質透過性を決定する選択分離層と、物理的に膜構造を維持する支持層からなって、支持層は多孔質構造であることが好ましい。

【0013】次に、前記特徴を有する膜の一実施態様として、中空糸膜について例示する。ポリスルホン系高分子およびPVPは市販のものを用いるが、ポリスルホン系高分子は可溶性環状二量体の含有率を下げるために、再沈殿法により精製する。ポリスルホン系高分子濃度が

1~1.0重量%になるように良溶媒、例えば、N,N-ジメチルアセトアミドに溶解し、この溶液を5.0~7.0℃に加温したエタノール中に滴下して、ポリスルホンを析出させる。可溶性環状二量体は上澄み液に溶解しているので、沈殿液をガラスフィルターで漏過し、フィルター上に残った沈殿物を加热乾燥することにより、ポリスルホンに対する可溶性環状二量体の含有率が1.0重量%以下のポリスルホン系高分子が得られる。

【0014】製膜原液の組成としては、ポリスルホン系高分子が1.0~2.0重量%、PVPが4~1.0重量%、およびこれらの溶剤からなる。PVPは分子量が大きい方が膜に残存しやすいので、重量平均分子量が1.0万以上のものを使用することが好ましい。溶剤はポリスルホン系高分子とPVPの共通溶剤であればよく、N,N-ジメチルアセトアミド、N,N-ジメチルホルムアミド、N-メチル-2-ピロリドン、ジメチルスルホキシド等が挙げられる。これらを単独、あるいは任意の割合で混合して使用することができる。また、凝固速度を調整するために、ポリマーが析出しない程度に水を添加してもよい。

【0015】中空糸膜を形成させるには、中空剤を使用する必要があるが、この組成は特に限定しない。水あるいは溶剤と水とを任意の割合で混合したものが好ましいが、アルコールや炭化水素を用いてもなんらさしつかえはない。上述の製膜原液と中空剤を環状オリフィスを有する二重巻糸金から吐出し、空中走行を経て凝固浴に導入する。凝固浴の組成は水でかまわない。凝固した中空糸膜をカセに巻き取って一定東長に切断した後、熱水洗浄を行い、さらに、1.0~5.0重量%のグリセリン水溶液を付着させて7.0~9.0℃で1.0時間以上熱風乾燥すれば、本発明の中空糸膜が得られる。

#### 【0016】

【発明の実施の形態】以下、実施例により本発明をさらに詳細に説明するが、本発明は、それらに限定されるものではない。なお、実施例で用いた諸数値は、以下の手順にて測定した。

(可溶性環状二量体の定量) 凍結乾燥した中空糸膜、あるいはポリスルホン系高分子0.1gをN-メチル-2-ピロリドン1.0ccで攪拌溶解した。溶解液をテフロン製のディスクフィルター(0.45ミクロン)で漏過した液をサンプルとした。測定は高速液体クロマトグラフ装置を用い、分子ふるいカラム(昭和電工(株)製: Shodex Asahipak GF-310 OHQ)に溶離液としてN,N-ジメチルホルムアミドを流速0.5cc/分で通液しながら、紫外線検出器における波長270nmでモニターした。一定量のサンプル液を注入し、オリゴマー領域に出てくる1.4~1.5分のピーク面積を求め、あらかじめ別途精製した可溶性環状二量体を用いて作成した検量線から、サンプル中の可溶性環状二量体含有率を算出した。

【0017】(膜表面の不溶性凝聚物の観察)凍結乾燥した中空糸膜を試料台に水平に固定し、斜めにスライスして膜内表面の一部を露出させた。銀蒸着した後、走査型電子顕微鏡(日立(株)製 S-530)により、倍率2000倍で内表面の不溶性凝聚物の存在状態を観察した。

$$PVP\text{濃度}(\%) = 100 \times C1 \times M1 / (C1 \times M1 + C2 \times M2) \quad (4)$$

式中の略号は以下の諸数値を示す。

C1: 究素原子濃度(重量%)

C2: 硫黄原子濃度(重量%)

M1: PVPの繰り返しユニットの分子量

M2: ポリスルホン系高分子の繰り返しユニットの分子量

【0019】(血小板付着試験)長さ15cmの中空糸膜50本を束ねて小型モジュールを作成し、該モジュールにヘパリン加ヒト新鮮血100ccを流速1.0cc/分にて15分間循環させた。生食でモジュールを洗浄後に中空糸膜を細断し、0.5%ポリエチレングリコールアルキルフェニルエーテル(商品名トリトンX100)含有生食中で超音波処理して、血小板から遊離した乳酸脱水素酵素(以下、LDHという)を定量した。LDHの定量は、LDHモノテスコット(ペーリンガー・マンハイム・山之内社製)を使用し、膜面積あたりのLDH活性として算出した。なお、陽性対照としてPVPを含有しない膜を用い、試験品と同時に比較した。

#### 【0020】

【参考例】ポリスルホン系高分子(Amoco社製:P-1700)1部をN,N-ジメチルアセトアミド(以下、DMAC)9部に加え、60°Cで2時間、攪拌溶解した。溶解液を70°Cに保温したエタノール100部に攪拌下で滴下し、終了後さらに1時間攪拌を続けた。再沈殿液をガラスフィルター(G1メッシュ)で吸引漉過し、残渣をエタノールで洗浄後に加熱乾燥して、精製ポリスルホン系高分子を得た。この可溶性環状二量体の含有率は0.3重量%であった。

#### 【0021】

【実施例1】参考例に示した精製ポリスルホン系高分子16部、およびPVP(BASF社製:K-90,分子量36万)4部をDMAC80部に添加し、50°Cで攪拌溶解して製膜原液を得た。中空剤はDMAC45部と水55部の混合液を用いた。この製膜原液と中空剤を5

【0018】(内表面のPVP濃度の測定)凍結乾燥した中空糸膜を試料台に固定して切開し、内表面を露出させた。X線光電子スペクトル測定装置(PHI-5400型)により表面深さ60オングストロームまでの窒素および硫黄原子の平均濃度を測定し、下記の式

(4)から内表面のPVP濃度を算出した。

0°Cに保温した二重歯糸口金から吐出させ、空中走行の後、50°Cの凝固浴を経てカセに巻き取った。東を熱水洗浄した後、20%グリセリン水溶液を付着させ、70°Cで12時間熱風乾燥して目的の膜を得た。得られた膜中の可溶性環状二量体含有率は0.2重量%であり、膜表面には不溶性凝聚物は観察されなかった。内表面のPVP濃度は3.3重量%であった。この膜のLDH活性は15.0U/m<sup>2</sup>と陽性対照(4.5, 5.0U/m<sup>2</sup>)に比較して低く、抗血栓性が優れていた。

#### 【0022】

【実施例2】参考例に示した精製ポリスルホン系高分子12部と未精製のポリスルホン系高分子6部、およびPVP(BASF社製:K-90,分子量36万)4部をDMAC80部に添加して、50°Cで攪拌溶解した。この製膜原液を用いた点以外は、すべて実施例1に従って膜を作成した。得られた膜中の可溶性環状二量体含有率は0.9重量%であり、膜表面には不溶性凝聚物は観察されなかった。内表面のPVP濃度は2.9重量%であった。この膜のLDH活性は18.4U/m<sup>2</sup>と陽性対照(4.5, 5.0U/m<sup>2</sup>)に比較して低く、抗血栓性が優れていた。

#### 【0023】

【比較例1】可溶性環状二量体の精製を行なわずに実施例1に従って膜を作成したところ、得られた膜中の可溶性環状二量体含有率は1.8重量%であり、膜表面には不溶性凝聚物が点在していた。内表面のPVP濃度は2.8重量%であった。この膜のLDH活性は39.8U/m<sup>2</sup>と陽性対照(4.5, 5.0U/m<sup>2</sup>)並みに高く、また、実施例に比較して有意に高値であった。

#### 【0024】

【発明の効果】本発明のポリスルホン系液体処理膜は、膜中の可溶性環状二量体の含有率が低く、不溶性凝聚物が膜表面に事实上存在しないため、血小板を活性化することなく抗血栓性に優れるものである。

# I. PATENT ABSTRACTS OF JAPAN

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## **(54) POLYSULFONE BLOOD TREATMENT MEMBRANE**

### **(57)Abstract:**

**PROBLEM TO BE SOLVED:** To improve antithrombotic properties by setting the content of a soluble cyclic dimer to a polysulfone polymer in a porous membrane at the specified value for the porous membrane composed of the polysulfone polymer and polyvinyl pyrrolidone utilized in the fields of hemodialysis, blood filtration and the like.

**SOLUTION:** In a porous blood treatment membrane composed of a polysulfone polymer and polyvinyl pyrrolidone(PVP), the content of a soluble cyclic dimer to the polysulfone polymer in the membrane is set at 1.0 wt.% or less. In the case the content of the soluble cyclic dimer in the membrane is set at the given value or less as described above, antithrombotic properties can be improved. For the PVP concentration of a membrane surface from the viewpoint of substance permeability, when PVP is contained too much, the lowering of pore radius of the membrane generated by swelling is remarkable and the permeation performance is lowered, while when it is too small, the filtration rate cannot be secured. The PVP concentration of the membrane surface brought into contact with blood, therefore, is preferably in the range of 25-50 wt.%.

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## CLAIMS

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[Claim(s)]

[Claim 1] Polysulfone system blood processing film characterized by the content of the fusibility annular dimer to the polysulfone system giant molecule in this film being 1.0 or less % of the weight in the porous membrane which consists of a polysulfone system giant molecule and a polyvinyl pyrrolidone.

[Claim 2] Polysulfone system blood processing film according to claim 1 characterized by the polyvinyl-pyrrolidone concentration in the blood contact surface being 25 - 50 % of the weight.

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## DETAILED DESCRIPTION

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[Detailed Description of the Invention]

[0001]

[Field of the Invention] This inventions are blood purification and a thing especially used in fields, such as hemodialysis, hemofiltration, and hemofiltration dialysis, about the film aiming at clearance of the wastes in blood by extracorporeal circulation.

[0002]

[Description of the Prior Art] In recent years, many membrane-separation techniques are put in practical use, and in order to separate the specified substance from the mixture of a liquid or a gas or to remove an impurity, various selection demarcation membranes are used. As a raw material of a selection demarcation membrane, generally the organic system macromolecule is used widely, for example, a polyacrylonitrile, a polyamide, polyimide, polyolefine, a polysiloxane, polysulfone, polymethacrylate, etc. are mentioned as a cellulose and synthetic macromolecule as naturally-occurring polymers. Although the polysulfone system macromolecule is broadly used as an industrial use demarcation membrane especially, the reason is because the resistance which was excellent to chemicals, such as a radiation, heating, and an acid, alkali, is shown. Moreover, since it excels also in biocompatibility or safety, recently, it is observed also as a raw material of a medical-application demarcation membrane, and need is increasing. However, although the fusibility annular dimer of polysulfone is contained in the polysulfone system macromolecule as one of the by-products accompanying a polymerization and it is dissolving immediately after adjustment of a film production undiluted solution, it crystallizes with time henceforth and becomes an insoluble aggregate. When this was incorporated as it was and deposited on the film front face, the platelet was activated at the time of contact into blood, and there was a possibility of reducing anti-thrombus nature as a result.

[0003]

[Problem(s) to be Solved by the Invention] This invention aims at offering the polysulfone system blood processing film which is excellent in anti-thrombus nature by making it an insoluble aggregate not included as a matter of fact on a film front face.

[0004]

[Means for Solving the Problem] In order that this invention persons may solve said technical problem, as a result of inquiring wholeheartedly, the amount of the insoluble aggregate which exists in that some fusibility annular dimers contained in 1 polysulfone system macromolecule crystallize with time, and it forms an insoluble aggregate and 2 film front face found out supporting the content of the fusibility annular dimer in the film. Although the detailed reason is not clear, when the content of the fusibility annular dimer to a polysulfone system macromolecule is high, the annular dimer which cannot dissolve in the chain of a polysulfone system macromolecule separates, and since it is unstable, that which condenses mutually and insolubilizes is presumed in a solvent. Therefore, when the content of the fusibility annular dimer in the film was below constant value, it turned out that the insoluble aggregate excels [ front face / film ] in anti-thrombus nature by private seal \*\* and such film as a matter of fact.

[0005] That is, this invention is characterized by the content of the fusibility annular dimer to the polysulfone system giant molecule in this film being 1.0 or less % of the weight in the porous blood processing film which consists of a polysulfone system giant molecule and a polyvinyl pyrrolidone (henceforth PVP). The first component which constitutes the film of this invention is a polysulfone system macromolecule. It may be the aromatic series polysulfone system macromolecule which has the following chemical structure type (1) or the repetitive construct which used (2) as the unit, and you may be the so-called polysulfone derivative with which the functional group and the alkyl group were added to the ring, and conversion polysulfone. In addition, Ar in a formula shows the bivalence phenyl group of the Para permutation. Especially the molecular weight of these polysulfone system macromolecule is not limited.

[0006]

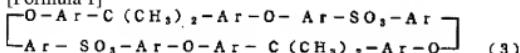
-O-Ar-C(CH<sub>3</sub>)<sub>2</sub>-Ar-O-Ar-SO<sub>3</sub>-Ar- (1)

-O-Ar-SO<sub>3</sub>-Ar- (2)

Bisphenol A and dichloro diphenylsulfone which are the fusibility annular dimer contained in a polysulfone system giant molecule, and are a polymerization raw material condense the second component dyad every by turns, and cyclize it. A chemical structure type is shown in following (3).

[0007]

[Formula 1]



[0008] The content of the fusibility annular dimer to a polysulfone system macromolecule melts the film or raw material resin to a solvent, and it is computed by carrying out quantitative analysis of it with high performance chromatography. Since a fusibility annular dimer does not dissolve in the coagulation bath or wash water which are usually used at all but is incorporated in the film as it is when producing a film by the general wet spinning method, this content in the film becomes 1.4 - 2.0 % of the weight. By such film, the deposit of an insoluble aggregate may be seen on a film front face.

[0009] Although, as for the film of this invention, hydrophilization of the film front face is carried out to homogeneity by PVP like the after-mentioned, since an insoluble aggregate does

not contain PVP, a film front face will be dotted with a hydrophobic, strong part. Moreover, if a film front face is dotted with an aggregate, the minute turbulence of a blood flow may arise on a part, and shearing stress may be applied to a platelet. As these results, activation of a platelet takes place and it is thought that membranous anti-thrombus nature falls. If the content of a fusibility annular dimer is 1.0 or less % of the weight, an insoluble aggregate is not observed as a matter of fact on a film front face, but since it is not dotted with a hydrophobic part, there will be no possibility that anti-thrombus nature may fall.

[0010] The method of obtaining the film with the low content of a fusibility annular dimer is not included under the category of this invention, but should just use a well-known means. However, film washing should be avoided, in order to carry out washing clearance simultaneously, to spoil the hydrophilic property on the front face of the film and for a part of PVP to cause blood coagulation, if it washes after film production. After the approach of producing a film after refining commercial polysulfone is desirable, for example, dissolves a polysulfone system macromolecule in a good solvent, to a polysulfone system macromolecule, it is a poor solvent and there is a method of making a fusibility annular dimer reprecipitate in the dissolving solvent, and moreover, collecting them. Moreover, after dissolving a polysulfone system macromolecule in a good solvent, about 1 - 5% of moisture is added, an insoluble aggregate is generated compulsorily, and how to carry out judgment clearance by filtration or centrifugal separation, the method of isolating preparatively further the fraction which does not contain a fusibility annular dimer with preparative chromatography, etc. are considered. Even if it chooses which approach, there is no inconvenience.

[0011] The third component which constitutes the film of this invention is PVP. The polysulfone system macromolecule itself has strong hydrophobicity, and it cannot get wet easily to aquosity media, such as blood or dialysing fluid. Moreover, a platelet is activated owing to hydrophobicity and blood coagulation tends to happen. Therefore, as blood processing film, hydrophilization of the film front face which contacts blood at least fully needs to be carried out. Even if it washes the film at a film production process, PVP is suitable as a neutral aquosity macromolecule which remains on a film front face to some extent, demonstrates a hydrophilic property, and moreover does not have unnecessary electrification.

[0012] On the other hand, the optimal range exists in the PVP concentration on the front face of the film from the point of matter permeability. If it exists superfluously, lowering of the pore radius of the film by swelling will be remarkable, matter permeability ability will fall, but filtration velocity is not securable even if too few. Therefore, as for the PVP concentration on the front face of the film in contact with blood, it is desirable that it is 25 - 50 % of the weight, and in order to gather the elimination factor of low-molecular protein, it is still more desirable [ concentration ] that it is 25 - 35 % of the weight. It does not limit especially about a membranous gestalt and does not interfere by the flat film or the hollow fiber, either. However, in order to secure efficient matter permeability, it consists of a selection detached core which determines matter permeability, and supporters who maintain membrane structure physically, and, as for supporters, it is desirable that it is porous structure.

[0013] Next, it illustrates about a hollow fiber as one embodiment of the film which has said description. Although a polysulfone system macromolecule and PVP use a commercial thing, a polysulfone system macromolecule is refined by the reprecipitating method, in order to lower the content of a fusibility annular dimer. It dissolves in a good solvent, for example, N,N-dimethylacetamide, so that polysulfone system giant-molecule concentration may become 1 - 10% of the weight, and it is dropped into the ethanol which warmed this solution at 50-70

degrees C, and polysulfone is deposited. Since the fusibility annular dimer is dissolving in the supernatant, 1.0 or less % of the weight of a polysulfone system macromolecule is obtained for the content of the fusibility annular dimer to polysulfone by filtering precipitate liquid with a glass filter and carrying out stoving of the precipitate which remained on the filter.

[0014] As a presentation of a film production undiluted solution, PVP consists [ a polysulfone system macromolecule ] of 4 - 10 % of the weight, and these solvents ten to 20% of the weight. Since the one where molecular weight is larger tends to remain on the film, as for PVP, it is desirable that weight average molecular weight uses 100,000 or more things. N,N-dimethylacetamide, N,N-dimethylformamide, a N-methyl-2-pyrrolidone, dimethyl sulfoxide, etc. are mentioned that solvents should just be a polysulfone system giant molecule and a common solvent of PVP. These can be mixed and used at a rate of independence or arbitration. Moreover, in order to adjust a coagulation rate, water may be added to extent in which a polymer does not deposit.

[0015] Although it is necessary to use a hollow agent in order to make a hollow fiber form, especially this presentation is not limited. Although what mixed water, or a solvent and water at a rate of arbitration is desirable, even if it uses alcohol and a hydrocarbon, there is no inconvenience in any way. An above-mentioned film production undiluted solution and an above-mentioned hollow agent are introduced into a coagulation bath through discharge and air transit from the duplex spinneret which has an annular orifice. Water is sufficient as the presentation of a coagulation bath. If perform hot water washing, 10 - 50% of the weight of a glycerol water solution is made to adhere further and hot air drying is carried out at 70-90 degrees C for 10 hours or more after rolling round the solidified hollow fiber to skein and cutting it to fixed bundle length, the hollow fiber of this invention will be obtained.

[0016]

[Embodiment of the Invention] Hereafter, although an example explains this invention to a detail further, this invention is not limited to them. In addition, many numeric values used in the example were measured in the following procedures.

(Quantum of a fusibility annular dimer) The churning dissolution of the hollow fiber which freeze-dried, or the 0.1g of the polysulfone system giant molecules was carried out by 100 cc of N-methyl-2-pyrrolidones. The liquid which filtered the solution by the disk filter made from Teflon (0.45 microns) was made into the sample. It acted as the monitor of the measurement on the wavelength of 270nm in an ultraviolet-rays detector, dipping N,N-dimethylformamide in a molecular sieve column (Showa Denko [ K.K. ] make: ShodexAsahipakGF-310HQ) by part for 0.5 cc/of the rates of flow as an eluate using high-speed liquid chromatograph equipment. The sample liquid of a constant rate was poured in, it asked for the peak area for 14 - 15 minutes which comes out to an oligomer field, and the fusibility annular dimer content in a sample was computed from the calibration curve created using the fusibility annular dimer refined separately beforehand.

[0017] (Observation of the insoluble aggregate on the front face of the film) The hollow fiber which freeze-dried was fixed at a level with a sample base, it sliced aslant, and a part of film internal surface was exposed. After carrying out silver vacuum evaporation, the insoluble aggregate's of internal surface existence condition was observed by one 2000 times the scale factor of this with the scanning electron microscope (made in Hitachi S-530).

[0018] (Measurement of the PVP concentration of an internal surface) It fixed to the sample base, the hollow fiber which freeze-dried was cut open, and the internal surface was exposed. The nitrogen to a surface depth of 60A and the average concentration of a sulfur atom were

measured with X linear-light electron-spectrum measuring device (PHI-5400 mold), and the PVP concentration of an internal surface was computed from the following formula (4).

PVP concentration (%) =  $100 \times C1 \times M1 / (C1 \times M1 + C2 \times M2)$  (4)

The code in a formula shows many following numeric values.

C1: Nitrogen atom concentration (% of the weight)

C2: Sulfur atom concentration (% of the weight)

M1 :P Molecular weight M2 of the repeat unit of VP: Molecular weight of the repeat unit of a polysulfone system macromolecule [0019] (Platelet adhesion trial) 50 hollow fibers with a die length of 15cm were bundled, the small module was created, and this module was made to circulate through ten cc of heparinized Homo sapiens fresh blood for 15 minutes in a part for 1.0 cc of the rates of flow. eating raw food -- after washing a module -- a hollow fiber -- beating -- carrying out -- 0.5% polyethylene-glycol alkylphenyl ether (trade name triton X100) content -- eating raw food -- it is inside, it ultrasonicated and the quantum of the lactate dehydrogenase (henceforth LDH) isolated from the platelet was carried out. The quantum of LDH used the LDH mono-test kit (Boehringer Mannheim and made in Yamanouchi), and computed it as LDH activity per film surface product. In addition, it compared with a specimen and coincidence using the film which does not contain PVP as positive control.

[0020]

[Related Example(s)] The polysulfone system giant-molecule (product made from Amoco--1700) 1 section was added to the N,N-dimethylacetamide (following, DMAC) 9 section, and the stirring dissolution was carried out at 60 degrees C for 2 hours. It was dropped at the ethanol 100 section which kept the solution warm at 70 degrees C under stirring, and stirring was continued after termination for further 1 hour. Suction filtration of the reprecipitation liquid was carried out with the glass filter (G1 mesh), stoving of the residue was carried out after washing by ethanol, and the purification polysulfone system macromolecule was obtained. The content of this fusibility annular dimer was 0.3 % of the weight.

[0021]

[Example 1] The purification polysulfone system macromolecule 16 section shown in the example of reference and the PVP(BASF [ A.G. ] make: K-90, molecular weight 360,000) 4 section were added in the DMAC80 section, the stirring dissolution was carried out at 50 degrees C, and the film production undiluted solution was obtained. The hollow agent used the mixed liquor of the DMAC45 section and the water 55 section. It was made to breathe out from this film production undiluted solution and the duplex spinneret which kept the hollow agent warm at 50 degrees C, and rolled round to skein through the 50-degree C coagulation bath after air transit. After carrying out hot water washing of the bundle, the glycerol water solution was made to adhere 20%, hot air drying was carried out at 70 degrees C for 12 hours, and the target film was obtained. The fusibility annular dimer content in the obtained film is 0.2 % of the weight, and the insoluble aggregate was not observed in a film front face. The PVP concentration of an internal surface was 33 % of the weight. The LDH activity of this film is 15.0 U/m<sup>2</sup>. As compared with positive control (45.5 U/m<sup>2</sup>), it was low, and anti-thrombus nature was excellent.

[0022]

[Example 2] The purification polysulfone system macromolecule 12 section shown in the example of reference, the polysulfone system macromolecule 6 non-refined section, and the PVP(BASF [ A.G. ] make: K-90, molecular weight 360,000) 4 section were added in the DMAC80 section, and the stirring dissolution was carried out at 50 degrees C. Except the point using this film production undiluted solution, the film was altogether created according to the

example 1. The fusibility annular dimer content in the obtained film is 0.9 % of the weight, and the insoluble aggregate was not observed in a film front face. The PVP concentration of an internal surface was 29 % of the weight. The LDH activity of this film is 18.4 U/m2. As compared with positive control (45.5 U/m2), it was low, and anti-thrombus nature was excellent. [0023]

[The example 1 of a comparison] When the film was created according to the example 1, without refining a fusibility annular dimer, the fusibility annular dimer content in the obtained film is 1.8 % of the weight, and the film front face was dotted with the insoluble aggregate. The PVP concentration of an internal surface was 28 % of the weight. The LDH activity of this film is 39.8 U/m2. It was high as much as positive control (45.5 U/m2), and a high price intentionally as compared with the example.

[0024]

[Effect of the Invention] The polysulfone system blood processing film of this invention has the low content of the fusibility annular dimer in the film, and since an insoluble aggregate does not exist in a film front face as a matter of fact, it excels in anti-thrombus nature, without activating a platelet.

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## TECHNICAL FIELD

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[Field of the Invention] This inventions are blood purification and a thing especially used in fields, such as hemodialysis, hemofiltration, and hemofiltration dialysis, about the film aiming at clearance of the wastes in blood by extracorporeal circulation.

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## PRIOR ART

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[Description of the Prior Art] In recent years, many membrane-separation techniques are put in practical use, and in order to separate the specified substance from the mixture of a liquid or a gas or to remove an impurity, various selection demarcation membranes are used. As a raw material of a selection demarcation membrane, generally the organic system macromolecule is used widely, for example, a polyacrylonitrile, a polyamide, polyimide, polyolefine, a polysiloxane, polysulfone, polymethacrylate, etc. are mentioned as a cellulose and synthetic macromolecule as naturally-occurring polymers. Although the polysulfone system macromolecule is broadly used as an industrial use demarcation membrane especially, the reason is because the resistance which was excellent to chemicals, such as a radiation, heating, and an acid, alkali, is shown. Moreover, since it excels also in biocompatibility or safety, recently, it is observed also as a raw material of a medical-application demarcation membrane, and need is increasing. However, although the fusibility annular dimer of polysulfone is contained in the polysulfone system macromolecule as one of the by-products accompanying a polymerization and it is dissolving immediately after adjustment of a film production undiluted solution, it crystallizes with time henceforth and becomes an insoluble aggregate. When this was incorporated as it was and deposited on the film front face, the platelet was activated at the time of contact into blood, and there was a possibility of reducing anti-thrombus nature as a result.

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## EFFECT OF THE INVENTION

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[Effect of the Invention] The polysulfone system blood processing film of this invention has the low content of the fusibility annular dimer in the film, and since an insoluble aggregate does not exist in a film front face as a matter of fact, it excels in anti-thrombus nature, without activating a platelet.

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## TECHNICAL PROBLEM

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[Problem(s) to be Solved by the Invention] This invention aims at offering the polysulfone system blood processing film which is excellent in anti-thrombus nature by making it an insoluble aggregate not included as a matter of fact on a film front face.

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## MEANS

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[Means for Solving the Problem] In order that this invention persons may solve said technical problem, as a result of inquiring wholeheartedly, the amount of the insoluble aggregate which exists in that some fusibility annular dimers contained in 1 polysulfone system macromolecule crystallize with time, and it forms an insoluble aggregate and 2 film front face found out supporting the content of the fusibility annular dimer in the film. Although the detailed reason is not clear, when the content of the fusibility annular dimer to a polysulfone system macromolecule is high, the annular dimer which cannot dissolve in the chain of a polysulfone system macromolecule separates, and since it is unstable, that which condenses mutually and insolubilizes is presumed in a solvent. Therefore, when the content of the fusibility annular dimer in the film was below constant value, it turned out that the insoluble aggregate excels [ front face / film ] in anti-thrombus nature by private seal \*\* and such film as a matter of fact.

[0005] That is, this invention is characterized by the content of the fusibility annular dimer to the polysulfone system giant molecule in this film being 1.0 or less % of the weight in the porous blood processing film which consists of a polysulfone system giant molecule and a polyvinyl pyrrolidone (henceforth PVP). The first component which constitutes the film of this invention is a polysulfone system macromolecule. It may be the aromatic series polysulfone system macromolecule which has the following chemical structure type (1) or the repetitive construct which used (2) as the unit, and you may be the so-called polysulfone derivative with which the functional group and the alkyl group were added to the ring, and conversion polysulfone. In addition, Ar in a formula shows the bivalence phenyl group of the Para permutation. Especially the molecular weight of these polysulfone system macromolecule is not limited.

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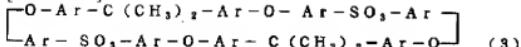
-O-Ar-C(CH<sub>3</sub>)<sub>2</sub>-Ar-O-Ar-SO<sub>3</sub>-Ar- (1)

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Bisphenol A and dichloro diphenylsulfone which are the fusibility annular dimer contained in a polysulfone system giant molecule, and are a polymerization raw material condense the second component dyad every by turns, and cyclize it. A chemical structure type is shown in following (3).

[0007]

[Formula 1]



[0008] The content of the fusibility annular dimer to a polysulfone system macromolecule melts the film or raw material resin to a solvent, and it is computed by carrying out quantitative analysis of it with high performance chromatography. Since a fusibility annular dimer does not dissolve in the coagulation bath or wash water which are usually used at all but is incorporated in the film as it is when producing a film by the general wet spinning method, this content in the film becomes 1.4 - 2.0 % of the weight. By such film, the deposit of an insoluble aggregate may be seen on a film front face.

[0009] Although, as for the film of this invention, hydrophilization of the film front face is carried out to homogeneity by PVP like the after-mentioned, since an insoluble aggregate does not contain PVP, a film front face will be dotted with a hydrophobic, strong part. Moreover, if a film front face is dotted with an aggregate, the minute turbulence of a blood flow may arise on a part, and shearing stress may be applied to a platelet. As these results, activation of a platelet takes place and it is thought that membranous anti-thrombus nature falls. If the content of a fusibility annular dimer is 1.0 or less % of the weight, an insoluble aggregate is not observed as a matter of fact on a film front face, but since it is not dotted with a hydrophobic part, there will be no possibility that anti-thrombus nature may fall.

[0010] The method of obtaining the film with the low content of a fusibility annular dimer is not included under the category of this invention, but should just use a well-known means. However, film washing should be avoided, in order to carry out washing clearance simultaneously, to spoil the hydrophilic property on the front face of the film and for a part of PVP to cause blood coagulation, if it washes after film production. After the approach of producing a film after refining commercial polysulfone is desirable, for example, dissolves a polysulfone system macromolecule in a good solvent, to a polysulfone system macromolecule, it is a poor solvent and there is a method of making a fusibility annular dimer reprecipitate in the dissolving solvent, and moreover, collecting them. Moreover, after dissolving a polysulfone system macromolecule in a good solvent, about 1 - 5% of moisture is added, an insoluble aggregate is generated compulsorily, and how to carry out judgment clearance by filtration or centrifugal separation, the method of isolating preparatively further the fraction which does not contain a fusibility annular dimer with preparative chromatography, etc. are considered. Even if it chooses which approach, there is no inconvenience.

[0011] The third component which constitutes the film of this invention is PVP. The polysulfone system macromolecule itself has strong hydrophobicity, and it cannot get wet easily to aquosity media, such as blood or dialysing fluid. Moreover, a platelet is activated owing to hydrophobicity and blood coagulation tends to happen. Therefore, as blood processing film, hydrophilization of the film front face which contacts blood at least fully needs to be carried out. Even if it washes the film at a film production process, PVP is suitable as a neutral aquosity macromolecule which remains on a film front face to some extent, demonstrates a hydrophilic property, and moreover does not have unnecessary electrification.

[0012] On the other hand, the optimal range exists in the PVP concentration on the front face of the film from the point of matter permeability. If it exists superfluously, lowering of the pore radius of the film by swelling will be remarkable, matter permeability ability will fall, but

filtration velocity is not securable even if too few. Therefore, as for the PVP concentration on the front face of the film in contact with blood, it is desirable that it is 25 - 50 % of the weight, and in order to gather the elimination factor of low-molecular protein, it is still more desirable [concentration] that it is 25 - 35 % of the weight. It does not limit especially about a membranous gestalt and does not interfere by the flat film or the hollow fiber, either. However, in order to secure efficient matter permeability, it consists of a selection detached core which determines matter permeability, and supporters who maintain membrane structure physically, and, as for supporters, it is desirable that it is porous structure.

[0013] Next, it illustrates about a hollow fiber as one embodiment of the film which has said description. Although a polysulfone system macromolecule and PVP use a commercial thing, a polysulfone system macromolecule is refined by the reprecipitating method, in order to lower the content of a fusibility annular dimer. It dissolves in a good solvent, for example, N,N-dimethylacetamide, so that polysulfone system giant-molecule concentration may become 1 - 10% of the weight, and it is dropped into the ethanol which warmed this solution at 50-70 degrees C, and polysulfone is deposited. Since the fusibility annular dimer is dissolving in the supernatant, 1.0 or less % of the weight of a polysulfone system macromolecule is obtained by the content of the fusibility annular dimer to polysulfone by filtering precipitate liquid with a glass filter and carrying out stoving of the precipitate which remained on the filter.

[0014] As a presentation of a film production undiluted solution, PVP consists [a polysulfone system macromolecule] of 4 - 10 % of the weight, and these solvents ten to 20% of the weight. Since the one where molecular weight is larger tends to remain on the film, as for PVP, it is desirable that weight average molecular weight uses 100,000 or more things. N,N-dimethylacetamide, N,N-dimethylformamide, a N-methyl-2-pyrrolidone, dimethyl sulfoxide, etc. are mentioned that solvents should just be a polysulfone system giant molecule and a common solvent of PVP. These can be mixed and used at a rate of independence or arbitration. Moreover, in order to adjust a coagulation rate, water may be added to extent in which a polymer does not deposit.

[0015] Although it is necessary to use a hollow agent in order to make a hollow fiber form, especially this presentation is not limited. Although what mixed water, or a solvent and water at a rate of arbitration is desirable, even if it uses alcohol and a hydrocarbon, there is no inconvenience in any way. An above-mentioned film production undiluted solution and an above-mentioned hollow agent are introduced into a coagulation bath through discharge and air transit from the duplex spinneret which has an annular orifice. Water is sufficient as the presentation of a coagulation bath. If perform hot water washing, 10 - 50% of the weight of a glycerol water solution is made to adhere further and hot air drying is carried out at 70-90 degrees C for 10 hours or more after rolling round the solidified hollow fiber to skein and cutting it to fixed bundle length, the hollow fiber of this invention will be obtained.

[0016] [Embodiment of the Invention] Hereafter, although an example explains this invention to a detail further, this invention is not limited to them. In addition, many numeric values used in the example were measured in the following procedures.

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molecular sieve column (Showa Denko [ K.K. ] make: Shodex Asahipak GF-310HQ) by part for 0.5 cc/of the rates of flow as an eluate using high-speed liquid chromatograph equipment. The sample liquid of a constant rate was poured in, it asked for the peak area for 14 - 15 minutes which comes out to an oligomer field, and the fusibility annular dimer content in a sample was computed from the calibration curve created using the fusibility annular dimer refined separately beforehand.

[0017] (Observation of the insoluble aggregate on the front face of the film) The hollow fiber which freeze-dried was fixed at a level with a sample base, it sliced aslant, and a part of film internal surface was exposed. After carrying out silver vacuum evaporation, the insoluble aggregate's of internal surface existence condition was observed by one 2000 times the scale factor of this with the scanning electron microscope (made in Hitachi S-530).

[0018] (Measurement of the PVP concentration of an internal surface) It fixed to the sample base, the hollow fiber which freeze-dried was cut open, and the internal surface was exposed. The nitrogen to a surface depth of 60A and the average concentration of a sulfur atom were measured with X linear-light electron-spectrum measuring device (PHI-5400 mold), and the PVP concentration of an internal surface was computed from the following formula (4).

PVP concentration (%) =  $100 \times C1 \times M1 / (C1 \times M1 + C2 \times M2)$  (4)

The code in a formula shows many following numeric values.

C1: Nitrogen atom concentration (% of the weight)

C2: Sulfur atom concentration (% of the weight)

M1 :P Molecular weight M2 of the repeat unit of VP: Molecular weight of the repeat unit of a polysulfone system macromolecule [0019] (Platelet adhesion trial) 50 hollow fibers with a die length of 15cm were bundled, the small module was created, and this module was made to circulate through ten cc of heparinized Homo sapiens fresh blood for 15 minutes in a part for 1.0 cc/of the rates of flow. eating raw food -- after washing a module -- a hollow fiber -- beating -- carrying out -- 0.5% polyethylene-glycol alkylphenyl ether (trade name triton X100) content -- eating raw food -- it is inside, it ultrasonicated and the quantum of the lactate dehydrogenase (henceforth LDH) isolated from the platelet was carried out. The quantum of LDH used the LDH mono-test kit (Boehringer Mannheim and made in Yamanouchi), and computed it as LDH activity per film surface product. In addition, it compared with a specimen and coincidence using the film which does not contain PVP as positive control.

[0020]

[Related Example(s)] The polysulfone system giant-molecule (product made from Amoco--1700) 1 section was added to the N,N-dimethylacetamide (following, DMAC) 9 section, and the stirring dissolution was carried out at 60 degrees C for 2 hours. It was dropped at the ethanol 100 section which kept the solution warm at 70 degrees C under stirring, and stirring was continued after termination for further 1 hour. Suction filtration of the reprecipitation liquid was carried out with the glass filter (G1 mesh), stoving of the residue was carried out after washing by ethanol, and the purification polysulfone system macromolecule was obtained. The content of this fusibility annular dimer was 0.3 % of the weight.

[0021]

[Example 1] The purification polysulfone system macromolecule 16 section shown in the example of reference and the PVP(BASF [ A.G. ] make: K-90, molecular weight 360,000) 4 section were added in the DMAC80 section, the stirring dissolution was carried out at 50 degrees C, and the film production undiluted solution was obtained. The hollow agent used the mixed liquor of the DMAC45 section and the water 55 section. It was made to breathe out from this

film production undiluted solution and the duplex spinneret which kept the hollow agent warm at 50 degrees C, and rolled round to skein through the 50-degree C coagulation bath after air transit. After carrying out hot water washing of the bundle, the glycerol water solution was made to adhere 20%, hot air drying was carried out at 70 degrees C for 12 hours, and the target film was obtained. The fusibility annular dimer content in the obtained film is 0.2 % of the weight, and the insoluble aggregate was not observed in a film front face. The PVP concentration of an internal surface was 33 % of the weight. The LDH activity of this film is 15.0 U/m<sup>2</sup>. As compared with positive control (45.5 U/m<sup>2</sup>), it was low, and anti-thrombus nature was excellent. [0022]

[Example 2] The purification polysulfone system macromolecule 12 section shown in the example of reference, the polysulfone system macromolecule 6 non-refined section, and the PVP(BASF [ A.G. ] make: K-90, molecular weight 360,000) 4 section were added in the DMAC80 section, and the stirring dissolution was carried out at 50 degrees C. Except the point using this film production undiluted solution, the film was altogether created according to the example 1. The fusibility annular dimer content in the obtained film is 0.9 % of the weight, and the insoluble aggregate was not observed in a film front face. The PVP concentration of an internal surface was 29 % of the weight. The LDH activity of this film is 18.4 U/m<sup>2</sup>. As compared with positive control (45.5 U/m<sup>2</sup>), it was low, and anti-thrombus nature was excellent. [0023]

[The example 1 of a comparison] When the film was created according to the example 1, without refining a fusibility annular dimer, the fusibility annular dimer content in the obtained film is 1.8 % of the weight, and the film front face was dotted with the insoluble aggregate. The PVP concentration of an internal surface was 28 % of the weight. The LDH activity of this film is 39.8 U/m<sup>2</sup>. It was high as much as positive control (45.5 U/m<sup>2</sup>), and a high price intentionally as compared with the example.

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[Translation done.]